REMARKS

STATUS OF THE APPLICATION

With this amendment, claims 4 and 10 have been amended. New claims 11-12 have been added. Claims 1-3 and 7-9 have been previously canceled. No new matter has been added with these claim amendments.

CLAIM REJECTIONS – 35 U.S.C. SECTION 103(a)

Claim 4 stands rejected under 35 U.S.C. Section 103(a) as being unpatentable over the article to Kirchengast et al. ("Kirchengast") in view of the article to Srivatsa et al. ("Srivatsa") for the same reasons as set forth in the previous Office Action mailed September 21, 2007, namely, that it would have been obvious to combine the endothelin blockers taught by Kirchengast with the selective $\alpha_v\beta_3$ integrin receptor antagonist taught by Srivatsa, and that one of ordinary skill in the art would have been motivated to do so because "the endothelin blockers are able to reduce neointima proliferation (i.e., restenosis) as taught by Kirchengast and because the $\alpha_v\beta_3$ antagonist resulted in a marked reduction in neointimal hyperplasia the leading cause of restenosis". Applicants respectfully traverse the Examiner's claim rejection.

Applicants have amended claim 4 to recite, "A pharmaceutical composition for the prevention of restenosis comprising an ET_A endothelin blocker and an $\alpha_v\beta_3$ integrin receptor antagonist." Neither Kirchengast nor Srivatsa, alone or in combination teach, "A pharmaceutical composition for the prevention of restenosis comprising an ET_A endothelin blocker and an $\alpha_v\beta_3$ integrin receptor antagonist." Rather, Kirchengast teaches the use of endothelin receptor

antagonists alone for the reduction of restenosis, and does not teach or suggest combining an ET_A endothelin blocker and an $\alpha_v\beta_3$ integrin receptor antagonist for the prevention of restenosis. Kirchengast teaches, by way of summary of previously published data, that several different endothelin antagonists have been tested in different models of existing restenosis in live animals. These results are summarized in Table 1 (page 553), where Kirchengast discloses that the endothelin receptor antagonist FR 139317 reduced neointima proliferation by 76% and that the endothelin receptor antagonist TAK 044 reduced neointima proliferation by 80%. It is taught on page 553 (right bottom paragraph) that a blockade of the endothelin receptor is responsible for the reduction of restenosis. Given the high degrees of reduction in neointimal proliferation exhibited by certain of the endothelin receptor antagonists described, one skilled in the art extracts the clear teaching that administration of an endothelin receptor antagonist itself, in the absence of any other compound, is alone sufficient to reduce restenosis. However, there is no indication in Kirchengast to use $\alpha_v\beta_3$ integrin receptor antagonists for the prevention of restenosis.

Srivatsa teaches an $\alpha_v\beta_3$ integrin blockade limiting neointimal hyperplasia and lumen stenosis following deep coronary arterial stent injury and does not teach or suggest combining an ET_A endothelin blocker and an $\alpha_v\beta_3$ integrin receptor antagonist for the prevention of restenosis. Srivatsa teaches that a blockade of $\alpha_v\beta_3$ integrin limits stenosis. It is stressed in multiple passages that this blockade is selective (see abstract, page 424 left middle, 426 left middle). Therefore, the $\alpha_v\beta_3$ blocking compound, XJ 735, inhibits only $\alpha_v\beta_3$ and nothing else. Srivatsa further teaches that selective $\alpha_v\beta_3$ antagonism is sufficient to inhibit neointimal growth and lumen stenosis. Accordingly, if $\alpha_v\beta_3$ antagonism is alone sufficient to inhibit neointimal growth and lumen stenosis, and the compound XJ 735 used in the study is selective for only $\alpha_v\beta_3$ this means

that use of an $\alpha_v\beta_3$ integrin receptor antagonist alone already solves the posed problem of reducing restenosis. Faced with this teaching, one skilled in the art learns that inclusion of any other compound is unnecessary to solve the posed problem. Thus, Srivatsa teaches away from combining another substance with an $\alpha_v\beta_3$ integrin receptor antagonist in reducing restenosis, since this problem is already solved by an $\alpha_v\beta_3$ integrin receptor antagonist alone. Srivatsa does not mention endothelin blockers and there is no suggestion or motivation in Srivatsa to combine its $\alpha_v\beta_3$ integrin receptor antagonist with an endothelin blocker as Applicants have done in order to prevent restenosis.

Thus, Kirchengast and Srivatsa teach that administration of either an endothelin receptor antagonist or an $\alpha_v\beta_3$ integrin receptor antagonist alone already sufficiently solves the problem of reducing restenosis. This being the case, one skilled in the art would not contemplate adding another compound. If one compound is already sufficient to treat a given disease, it is illogical, and indeed impractical from a regulatory standpoint, to introduce another compound into the mix. Even if one skilled in the art could theoretically have combined the teachings of Kirchengast and Srivatsa, one skilled in the art would not have, and would have instead relied on the justifiable assurance that either the endothelin receptor antagonist of Kirchengast or the $\alpha_v\beta_3$ integrin receptor antagonist of Srivatsa would adequately solve the posed problem alone. Applicants submit that the reconstruction of the prior art to obtain Applicants' claimed invention requires impermissible hindsight.

The essence of Applicants' invention lies in the nonobvious combination of an endothelin receptor antagonist and an $\alpha_v\beta_3$ integrin receptor antagonist to achieve a sysnergistic effect in preventing restenosis. Applicants' invention permits the use of each component at a dose less than the dose useful alone, with a reduction in side effects (see specification, page 4, lines 23-27

and page 20, lines 24-30). Applicants' Example 5 (page 17, line 46 to page 18, line 6) shows that "the combination of ET receptor antagonists and $\alpha_v\beta_3$ integrin receptor antagonist represent a more effective means of preventing restenosis than treatment with either drug alone. In fact, given the higher predictive value of the pig restenosis model, the in vitro results suggest effective prevention of human restenosis with combinations of ET receptor antagonists and $\alpha_v\beta_3$ integrin receptor antagonist only, rather than monotherapy." This example clearly demonstrates that a combination of an endothelin blocker and an $\alpha_v\beta_3$ integrin receptor antagonist reduces coronaria restenosis in a pig model and therefore such combination is a factual basis for the prediction made in the claims and such combination has a clear synergistic effect. The present example provides factual support for the synergistic combination of an endothelin blocker and an $\alpha_v\beta_3$ integrin receptor antagonist for the prevention of restenosis.

Additionally, the present application refers to a comparative experiment (see page 18, line 35 to page 20, line 30) displaying that in fact synergistic effects have been observed when administering an endothelin blocker along with an $\alpha_v\beta_3$ integrin receptor antagonist in the prevention of restenosis in an animal model. Thus, the combination of an endothelin blocker and an $\alpha_v\beta_3$ integrin receptor antagonist is not a mere selection from the prior art but is based on experimental data. The Examiner is in effect stating that in the absence of data supporting this synergistic effect, the contended synergism cannot be believed to actually exist. However, the simple lack of experimental data supporting a statement in a patent application does not render said statement invalid or untrue. Rather, the value of such a statement must be examined with regard to the nature of the invention as well as the prior art cited. The originally filed application gives no reason to doubt the existence of the asserted synergistic effect between an ET_A endothelin blocker and an $\alpha_v\beta_3$ integrin receptor antagonist in preventing restenosis.

Thus, it would not be obvious to combine Kirchengast and Srivatsa to arrive at Applicants' claimed invention. The prior art does not provide any indication that a particular combination of an ET_A endothelin blocker and an $\alpha_v\beta_3$ integrin receptor antagonist may be used for the prevention of restenosis. Even if one skilled in the art did combine the teachings of Kirchengast and Srivatsa, one would still not arrive at Applicants' claimed invention.

Claim 10 stands rejected under 35 U.S.C. Section 103(a) as being unpatentable over Kirchengast in view of Srivatsa and further in view of U.S. Patent No. 4,761,406 to Flora et al. ("Flora") for the same reasons as set forth in the previous Office Action mailed September 21, 2007, namely, that it would have been obvious to combine the endothelin blockers taught by Kirchengast with the selective $\alpha_v\beta_3$ integrin receptor antagonist taught by Srivatsa in a kit format as taught by Flora. The Examiner states in the September 21, 2007 Office Action that Flora "teaches kits which facilitate the necessary strict compliance with methods of treatments". Applicants respectfully traverse the Examiner's claim rejection.

Applicants have amended claim 10 to recite, "A pharmaceutical trade package comprising an ET_A endothelin blocker and an $\alpha_v\beta_3$ integrin receptor antagonist as pharmaceutical agents and instructions for use of these pharmaceutical agents in combination for simultaneous, separate or temporal graduated administration for the prevention of restenosis." Neither Kirchengast, Srivatsa, nor Flora, either alone or in combination teach, "A pharmaceutical trade package comprising an ET_A endothelin blocker and an $\alpha_v\beta_3$ integrin receptor antagonist as pharmaceutical agents and instructions for use of these pharmaceutical agents in combination for simultaneous, separate or temporal graduated administration for the prevention of restenosis." Rather, as discussed above, Kirchengast teaches only the use of endothelin receptor antagonists, and Srivatsa teaches only the use of $\alpha_v\beta_3$ integrin receptor antagonists. Flora teaches a method

and kit for treating or preventing osteoporosis. There is no teaching or suggestion in Kirchengast or Srivatsa to combine their respective endothelin receptor antagonists or $\alpha_v\beta_3$ integrin receptor antagonists with the kit of Flora to obtain Applicants' claimed invention. Thus, it would not be obvious to combine Kirchengast, Srivatsa and Flora to arrive at Applicants' claimed invention.

New claim 11 further defines claim 4 "for the prevention of restenosis after vessel injury or revascularisation treatment". New claim 12 further defines claim 10 "for the prevention of restenosis after vessel injury or revascularisation treatment". Support for new claims 11 and 12 can be found in the specification at page 13, lines 27-28.

Applicants respectfully submit that neither Kirchengast, Srivatsa, nor Flora, alone or in combination, teach all of the features of independent claims 4 and 10, as amended, and Applicants' claimed invention is not obvious over Kirchengast in view of Srivatsa and further in view of Flora. Since dependent claim 11 depends from independent claim 4, and dependent claim 12 depends from independent claim 10, dependent claims 11 and 12 are not obvious over Kirchengast in view of Srivatsa and further in view of Flora either.

Thus, it would not be obvious to one skilled in the art to combine Kirchengast with Srivatsa and Flora to arrive at Applicants' claimed invention. Applicants respectfully request that the rejection of claims 4 and 10 as being obvious under 35 U.S.C. §103(a) be withdrawn.

CONCLUSION

Claims 4 and 10-12 are currently pending in the subject application. In view of the claim amendments and remarks set forth above, Applicants submit that the subject application is in condition for allowance and respectfully requests reconsideration and withdrawal of all the claim rejections.

Should the Examiner have any questions or should the Examiner wish to discuss any matters in connection with the subject application, the Examiner is invited to contact the undersigned.

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